AWARD NUMBER: W81XWH-15-1-0490

TITLE: Diagnosing Contributions of Sensory and Cognitive Deficits to Hearing Dysfunction in Blast-Exposed/ TBI Service Members

PRINCIPAL INVESTIGATOR: Dr. Barbara Shinn-Cunningham

CONTRACTING ORGANIZATION: Trustees of Boston University
Boston, MA 02215-1703

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Fort Detrick, Maryland 21702-5012

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5b. GRANT NUMBER
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6. AUTHOR(S)
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5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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13. SUPPLEMENTARY NOTES

14. ABSTRACT ***brief (~200 word) unclassified summary of most significant finding during the research period***
This project utilizes behavioral and electrophysiological methods to investigate peripheral and central contributions to auditory dysfunction. In fiscal year 1, IRB protocols have been fully approved at all levels, and CRADA approval between Boston University (Site 1, BU) and Walter Reed National Military Medical Center (Site 2, WRNMMC) has been arranged through the Geneva Foundation. The project has hired a full-time research audiologist, Dr. Lynn Bielski, who has been working closely with Mr. Scott Bressler from BU. To date, the electroencephalography (EEG) equipment has been installed at WRNMMC, and is running finalized versions of both the auditory and visual selective attention tasks. Subject recruitment has started, and while some experimental sessions yielded incomplete data sets, these issues have been addressed and the main focus for the next fiscal period will focus primarily on subject screening, data collection, and data analysis.

15. SUBJECT TERMS
IRB protocol approval, CRADA approval, EEG hardware and software setup and validation, Research Audiologist hire, subject recruitment

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1) INTRODUCTION:

Blast-exposed Service Members returning from recent conflicts in Afghanistan and Iraq pose a new, challenging problem for the audiological community—many have near-normal hearing thresholds, but have difficulty understanding speech amidst competing sounds. Many of these Service Members have been diagnosed with Central Auditory Processing Disorder (CAPD) or cognitive deficits. Exposure to blast likely plays a role in hearing dysfunction, and has also been linked to cognitive dysfunction with and without a confirmed diagnosis of traumatic brain injury. These two independent factors likely cause CAPD symptoms, one related to supra-threshold auditory coding fidelity and the other to cortical control of attentional processes related to the perception of sound, both of which can be adversely affected by exposure to blast. The goals of this study are to use objective electrophysiological tests to quantify specific sensory and cognitive deficits contributing to CAPD, to determine how these are related to blast exposure, and to develop a clinically useful test battery to quantify each of these deficits.

2) KEYWORDS:

Blast exposure, CAPD, traumatic brain injury, hearing loss, cochlear neuropathy, electroencephalography, frequency following response, auditory brainstem response

3) ACCOMPLISHMENTS:

Progress for Award W81XWH-15-1-0490 "Diagnosing Contributions of Sensory and Cognitive Deficits to Hearing Dysfunction in Blast-Exposed/TBI Service Members" for the time period September 15th, 2015 to September 14th, 2016 has been largely on schedule and hitting its milestones as summarized in the Statement of Work.

What were the major goals of the project?

The major goals applicable for the first year of the project all focused on putting into place all of the administrative and technical resources necessary to begin subject recruiting and data collection, and can be categorized as follows:

- **Preparation and review of research protocols for IRB approval (SOW Major Task 1)**
  The research protocol used in this award is part of a pre-existing **master protocol** for a multi-site CAPD prevalence study currently underway at the Walter Reed National Military Medical Center (WRNMMC), VA San Diego, and VA San Antonio. The main goal of Major Task 1 was to amend the existing protocol at Walter Reed and submit it for both IRB and second-level military IRB approval.

- **Hiring and training of Research Audiologist (SOW Major Task 2)**
  This included properly advertising the position, and interviewing potential candidates for the position. Once hired, we allotted 4-5 months to train the Research Audiologist on the screening and inclusion criteria for the study and procedures for data collection on the electroencephalography (EEG) equipment.

- **Development of electrophysiology test system (SOW Major Task 3)**
  This included acquiring all the necessary hardware components (EEG system, digital-to-audio interface, insert-earphones, supporting computers, and cabling). Approximately 2-3 months was set aside for installation and validation of the hardware set up, with an additional month provided for development and improvement of existing experimental software.

- **Oversight and administration of the project (SOW Major Task 6)**

- **Participant recruitment and evaluation (SOW Major Task 4)**
  We anticipated recruitment and consent of the first research subject to happen by month 9-10.

What was accomplished under these goals?

- **Preparation and review of research protocols for IRB approval (SOW Major Task 1)**
  01-Dec-2015: Initial first-level protocol approval obtained.
  Although the award is a collaboration between WRNMMC and Boston University (BU), it was determined that the research protocol only need approval at WRNMMC.

  02-Dec-2015: A Site-Specific Protocol Application (SSA) detailing specific language for the consent documents for blast and control group was approved by the WRNMMC IRB.

  25-Feb-2016: Second-level HRPO process finalized and approved allowing BU to receive de-identified data from WRNMMC.

- **Hiring and training of Research Audiologist (SOW Major Task 2)**

  Dr. Lynn Bielski was hired as the project Research Audiologist. Although her official start date was 01-July-2015, she has been involved with the project since the beginning. Dr. Bielski's training on the EEG equipment began when the EEG hardware was delivered by Mr. Bressler the week of 14-Mar-2016. As of the writing of this report, Dr. Bielski is now proficient in EEG data collection and preliminary data processing and analysis. Mr. Bressler and Dr. Bielski continue to work together on additional EEG data analysis techniques.

- **Development of electrophysiology test system (SOW Major Task 3)**

  Dec-2015: BioSemi EEG system and TDT RZ6 audio processor hardware ordered
  25-Jan-2016: Received delivery on BioSemi 32-channel EEG system
  11-Feb-2016: Received delivery on TDT RZ6 Auditory Workstation
  10-Feb-2016 to 11-Feb-2016:
  Mr. Bressler visited WRNMMC to assess the layout of the lab space and determined how the new hardware components were to be installed and integrated into the existing computer/equipment setup.
  28-Feb-2016: EEG hardware components assembled and tested at Boston University

  Mr. Bressler traveled to WRNMCC four additional times to train WRNMMC staff and implement software and experimental design improvements. Details of these trips are as follows:

  14-Mar-2016 to 18-Mar-2016
  - EEG system delivered to WRNMMC and installed.
  - Experimental software modified to conform with existing WRNMMC computer setup.

  19-Apr-2016 to 22-Apr-2016
  - Installed software upgrades to experimental scripts to improve ease of use
  - WRNMMC staff received introductory training on EEG data collection and analysis. Staff trained include: Dr. Lynn Bielski, Dr. Olga Stakhovskaya, Mr. General Lee, Dr. Lina Kubli, Dr. Melissa Kokx-Ryan, Dr. Ashley Zaleski, and Dr. Lee Ann Horvat
  - Pilot testing performed on auditory brainstem (ABR), envelope frequency following response (FFR), and auditory (ASA) and visual selective attention (VSA) tasks.

  6-Jun-2016 to 10-Jun-2016
  - Connected WRNMMC to the BU Cluster computing service allowing easy transfer of de-identified EEG data to BU. WRNMMC's cluster computing account also give them access to BU site license copies of MATLAB and other data analysis software packages.
  - Conducted additional EEG data collection and analysis training session focused on EEG experimental design, stimulus presentation, and time-synchronous data collection.

  15-Aug-2016 to 19-Aug-2016
  - Installed improved version of the Visual Selective Attention (VSA) task, which now includes 4 additional interfering stimuli positioned symmetrically and radially from center.
  - Piloted new VSA design on two WRNMMC staff volunteers
  - Further software improvements installed for both ASA and VSA task, including the ability to pause and re-start mid-session, running each task in demonstration mode

- **Oversight and administration of the project (SOW Major Task 6)**

  09-Dec-2015: Details of the sub-award between Boston University and the Geneva Foundation were finalized. This agreement provided the outlined how funds from the award recipient (Boston University) were to be transferred to WRNMMC through the Geneva Foundation.

  01-May-2016: Signed CRADA making funds available to WRNMMC through the Geneva Foundation.

  Dr. Bielski and Mr. Bressler continue to have an open line of communication as necessary to update each other on progress and potential pitfalls ensuring the future success of the project.

- **Participant recruitment and evaluation (SOW Major Task 4)**

  To date, we have screened a total of 18 potential study participants. Out of these subjects:

9 were eligible CONTROL subjects
4 were eligible BLAST-EXPOSED subjects
3 did not meet the study's eligibility criteria
2 did not return after their initial screening

All study participants have completed the Behavioral Test Session (BTS) battery.

For the Electrophysiological Test Session (ETS):
6 out of 9 CONTROL subjects and 3 out of 4 BLAST-CONTROL subjects have completed the Auditory Selective Attention task
5 out of 9 CONTROL subjects and 2 out of 4 BLAST-EXPOSED subjects have complete the Visual Selective Attention with simultaneous Suprathreshold Coding Fidelity (STCF) test

- **Other accomplishments not specifically detailed in the Statement of Work**
  Updates were made on the pre-existing equipment used in the Behavioral Test Session (BTS)

What opportunities for training and professional development has the project provided?
19-Jun-2016 to 20-Jun-2016: Six members of the WRNMMC team attended the Frequency Following Workshop hosted by the Auditory Neuroscience Laboratory and the Center for Computational Neuroscience and Neural Technologies (CompNet) at Boston University, Boston, MA. This workshop brought together leaders in the field of peripheral auditory processing, auditory brainstem physiology, and neural imaging to share the current state of their research endeavors. It featured two days of talks by invited speakers and poster sessions from a collection of submitted abstracts.

The working relationship between Dr. Bielski and Mr. Bressler has been, and continues to be, a mutually beneficial one. Dr. Bielski has gained valuable training in electroencephalography experimental design, data collection, and data analysis techniques. Mr. Bressler has also been providing instruction and guidance with more advanced coding principles in MATLAB. In return, Mr. Bressler is receiving exposure to translational research in a clinical setting. His interactions with Dr. Bielski, Dr. Ken Grant and other WRNMMC Audiology staff broaden his knowledge in auditory neuroscience, and provides him the unique opportunity to regularly interact and network with other leading researchers in his field.

How were the results disseminated to communities of interest?
Nothing to report

What do you plan to do during the next reporting period?
Now that the details of all of the experimental paradigms have been finalized the next reporting period will focus on subject recruitment and data collection. Dr. Bielski and Mr. Bressler will be analyzing the data in real time, and will continue to communicate regularly to ensure the project progresses in the right direction and remains on schedule.

4) IMPACT:

Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report

What was the impact on other disciplines?
Nothing to report

What was the impact on technology transfer?
Nothing to report

What was the impact on society beyond science and technology?
Nothing to report

5) CHANGES/PROBLEMS:

Changes in approach and reasons for change

The Visual Selective Attention task was improved from the design described in the original proposal. Initially, the visual task contained three flashing arrow stimuli to match the three melodic streams in the Auditory Selective Attention task. Dr. Grant suggested additional interfering stimuli be added to increase the level of visual intrusion to address possible problems with subjects directly foveating to the target sequence. The original visual task had two flashing arrow streams to the right and left of a central fixation point plus a third distractor arrow stream immediately above the fixation point. The new version places two addition arrow stimuli 45° to the right and left of the upper arrow position which are duplicated radially 180° away at similar positions below the central fixation point. The presentation pattern of the distracting arrow sequence changes once every second such that only one 0°-180° arrow pair changes their angular position at a time. This design change still permits us to distinguish the individual visually evoked neural responses to the onset of each stimulus change while increasing the amount of visual intrusion of the distracting sequence. The presentation pattern of the target left/right arrow streams was unchanged. The team at BU has independently tested this new paradigm on normal vision and/or corrected vision subject volunteers, and has verified similar patterns of neural responses to the older 3-stimulus design. As before, this visual task also presents sinusoidally amplitude modulated transposed up to 4096 Hz to simultaneously capture the envelope frequency following response in the auditory brainstem.

Actual or anticipated problems or delays and actions or plans to resolve them

The project is currently behind on its spending projections. The primary reason for this delay is because WRNMMC's access to funds was held up during the CRADA approval process through US Military Research and Materiel Command (MRMC). The CRADA approval was signed only 4 months ago on 01-May-2016, and delayed the hiring of Dr. Lynn Bielski by approximately 7 months. Her official start date was 01-July-2016; therefore, a portion of the spending shortfall is reflected in this 7-month salary gap. Additionally, Dr. Shinn-Cunningham did not draw her salary share from the award this fiscal year. During setup period and IRB/CRADA modifications, less of Dr. Shinn-Cunningham's input was required, and her 10% effort was covered by other available funding sources. Now that data are being collected and analyzed, her involvement will increase to the anticipated levels.

Due to the technical nature of the EEG setup we fully anticipated to have problems related to 1) unexpected errors in the stimulus presentation software and 2) lack of proficiency due to inexperience from the research staff at WRNMMC. As a result of these expected technical issues, we have incomplete EEG datasets for the first few study participants.

Dr. Bielski and Mr. Bressler have been in constant communication regarding software bugs, and have a system in place where Mr. Bressler can implement fixes locally at BU and pass them along for Dr. Bielski to install at WRNMMC. Furthermore, Mr. Bressler's trips in April, June, and August were scheduled to specifically deal with hardware and software issues beyond the scope of Dr. Bielski's expertise. As of the writing of this report, the EEG system is fully functioning and data collection is running smoothly without issue.

Initial attempts at collecting EEG subject data from the selective attention tasks were partially successful due to subjects' scheduling limitations. All potential study participants are active duty Service Members, and must schedule their appointments outside of their active duty responsibilities. We had originally planned for two sessions in order to collect the full complement of experimental data, but have now allowed for the possibility of additional sessions. With additional sessions we may observe a drop in subject compliance, but will address these issues if and when they arise.

We are also currently awaiting approval on an IRB amendment to insert language into the consent documents informing subjects that we intend to share their de-identified data with the FITBIR database. Progress on this front has been slow due to complications surrounding the Walter Reed portion of the larger multi-site master protocol to which this current project is attached. This multi-site project mandates all protocol amendments must receive approval from the all affiliated research sites; however, since WRNMMC is the only site collecting data that will be shared with FITBIR, we are currently negotiating local approval for this amendment. We fully expect this issue to be resolved within the next reporting quarter.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

6) PRODUCTS:

Publications, conference papers, and presentations

Bressler, S., Bonacci, L., Kwasa, J.A., and Shinn-Cunningham, B.G., "Attention-modulated Neural Responses to a Dynamic Visual Selective Attention Task," *Neuroscience 2015: 45th Annual Meeting of the Society for Neuroscience,* Chicago, IL, October 17-21, 2015.

Website(s) or other Internet sites(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other products

Nothing to report

7) PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project

Name:	Prof. Barbara Shinn-Cunningham
Project Role:	Co-Principal Investigator
Research Identifier:	0000-0002-5096-5914
Nearest person month worked:	1
Contribution to project:	
Funding support:	

Name:	Dr. Kenneth Grant
Project Role:	Co-Principal Investigator
Research Identifier:	
Nearest person month worked:	1
Contribution to project:	
Funding support:	

Name:	Scott Bressler
Project Role:	Research Engineer/Graduate Student
Research Identifier:	
Nearest person month worked:	12
Contribution to project:	Mr. Bressler is responsible for the procurement and installation the research hardware, development of the experimental and data analysis software, and training Research Audiologist, Dr. Bielski, in EEG data collection and analysis techniques. He has also been instrumental in filing the quarterly technical progress reports.
Funding support:	

Name:	Dr. Lynn Bielski
Project Role:	Research Audiologist
Research Identifier:	
Nearest person month worked:	7
Contribution to project:	Dr. Bielski is responsible for subject scheduling, evaluation, data collection, and data archiving. She represents the main point of contact for the study participants, and is Mr. Bressler's direct contact of all technical and/or equipment related issues.
Funding support:	

Name:	General Lee
Project Role:	Engineer
Research Identifier:	
Nearest person month worked:	1
Contribution to project:	Mr. Lee has provided assistance with the installation and maintenance of all of the EEG hardware and software resources, including, but not limited to, data storage and transfer, software debugging and troubleshooting, software licensing. Additionally, he has been instrumental in providing Mr. Bressler with the proper credentials in order to have access to WRNMMC.
Funding support:	

Name:	Dr. Leonard Varghese
Project Role:	Engineer
Research Identifier:	
Nearest person month worked:	1
Contribution to project:	Dr. Varghese provided valuable technical support and guidance in the acquisition, setup, and calibration of the EEG hardware and software system.
Funding support:	

Name:	Dr. Olga Stakhovskaya
Project Role:	Engineer
Research Identifier:	
Nearest person month worked:	1
Contribution to project:	Dr. Stakhovskaya has provided valuable technical support of the EEG hardware and software infrastructure.
Funding support:	CAPD Prevalence Study

Name:	Dr. Melissa Kokx-Ryan
Project Role:	Audiologist
Research Identifier:	
Nearest person month worked:	3
Contribution to project:	Dr. Kokx-Ryan has been involved in subject screening and collection of the ABR data.
Funding support:	CAPD Prevalence Study

Name:	Dr. Lina Kubli
Project Role:	Audiologist/Primary Investigator
Research Identifier:	
Nearest person month worked:	11
Contribution to project:	Dr. Kubli was a lead investigator responsible for Phases I & II of the CAPD Prevalence Study to which the BU study is attached. She recently accepted a new position in Aug-2016, and is no longer affiliated with the study.
Funding support:	CAPD Prevalence Study

Name:	Dr. Lee Ann Horvat
Project Role:	Audiologist
Research Identifier:	
Nearest person month worked:	11
Contribution to project:	Dr. Horvat was an audiologist responsible for Phases I & II of the CAPD Prevalence Study to which the BU study is attached. She also recently accepted a new position in Aug-2016, and is no longer affiliated with the study.

Funding support:	CAPD Prevalence Study

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

What other organizations were involved as partners?
Nothing to report

8) SPECIAL REPORTING REQUIREMENTS

Collaborative awards
Nothing to report

Quad charts

Diagnosing contributions of sensory and cognitive deficits to hearing dysfunction in blast-exposed / TBI Service Members

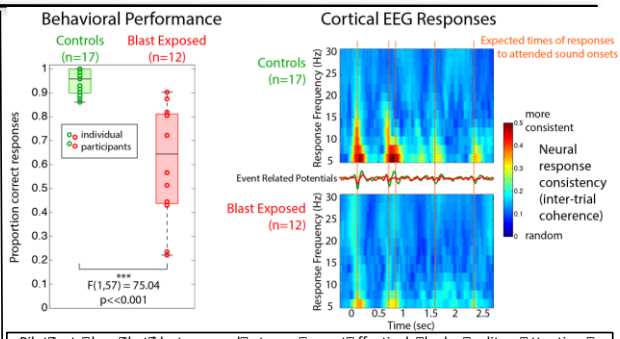
PI: Barbara G. Shinn-Cunningham **Org:** Boston University (sub: Walter Reed Nat. Mil. Med. Cent.) **Award Amount:** $1,500,000

Study/Product Aim(s)

- Understand why roughly 40% of blast-exposed Service Members returning from Iraq or Afghanistan (~15% of all personnel) experience difficulty understanding speech in noisy environments, despite having normal to near-normal hearing thresholds. These individuals are often misdiagnosed as having no hearing deficit, and are thus offered no treatment plan.
- Develop an efficient battery of tests appropriate for clinical use to diagnose patterns of hearing dysfunction in individual Service Members.

Approach

We will recruit Service Members with varying degrees of blast exposure. Using both behavioral measures and physiological biomarkers, we will quantify 1) supra-threshold coding fidelity (likely related to noise and possibly blast exposure), and 2) cognitive / executive function (likely related to blast exposure). We will quantify the relationships amongst communication deficits, blast exposure history, sensory hearing fidelity, and cognitive / cortical control deficits. We will develop a clinically appropriate test battery to diagnose and tease apart contributions of sensory and cognitive deficits to hearing dysfunction in individual Service Members.



Pilot tests show that blast-exposed veterans cannot effectively deploy auditory attention, as evidenced by behavioral deficits (re: controls; left) and weak cortical responses to attended sounds (right). Both sensory and cognitive deficits likely contribute to this dysfunction.

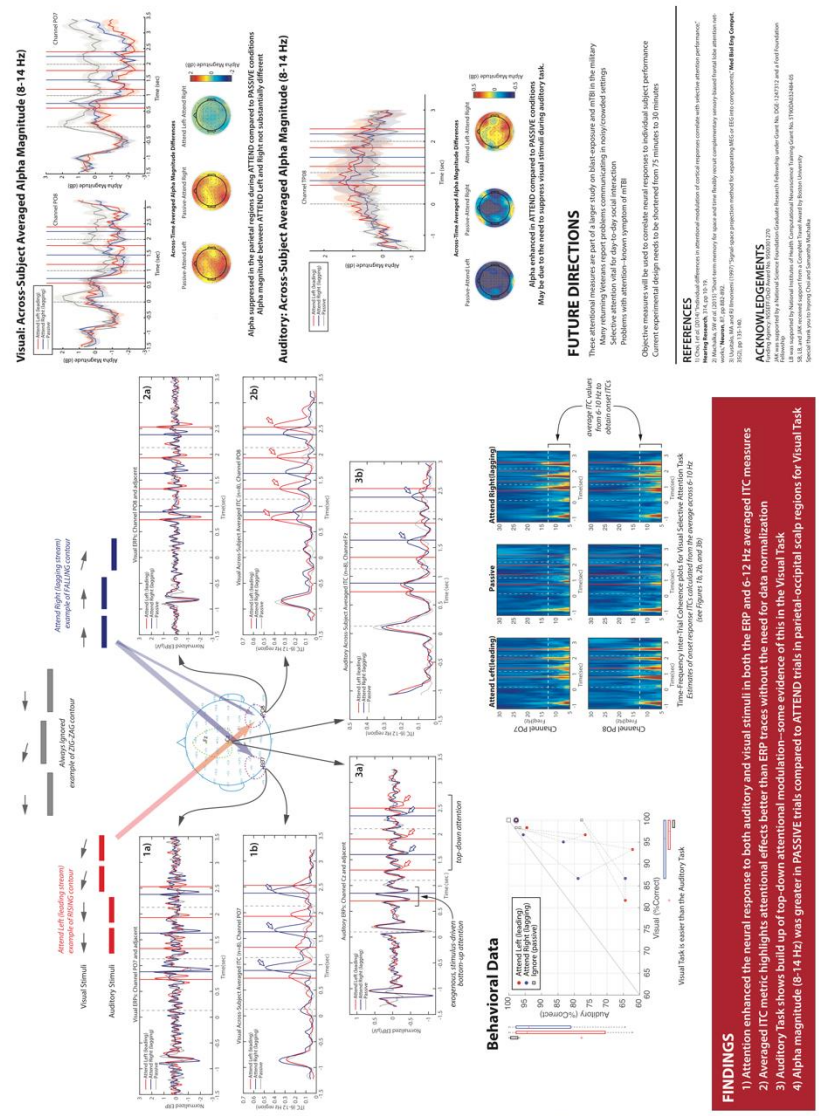
Timeline and Cost

Activities CY	16	17	18
Prepare for data collection			
Recruit and test ~50 subjects			
Model key relationships in results			
Develop efficient diagnostic battery			
Estimated Budget ($K)	**$528**	**$470**	**$484**

Updated: (15 September 2016)

Goals/Milestones
CY16 Goals – Setup and study initiation
☑ Hire and train research audiologist at WRNMMC
☑ Collect data on ~16 subjects (full set on ~12)
☐ Present preliminary results and solicit feedback
CY17 Goals – Data collection and dissemination
☐ Collect data on ~36 subjects (full set on ~27)
☐ Develop statistical model of key factors leading to hearing dysfunction
☐ Present results and solicit feedback
CY18 Goals – Wrap up and dissemination
☐ Finish data collection on ~18 subjects (full set on ~11)
☐ Finalize statistical analysis and modeling
☐ Develop efficient test battery for individualized diagnosis of specific sensory and cognitive deficits contributing to auditory dysfunction

Budget Expenditure to Date
Projected Expenditure: $528,411
Actual Expenditure: $345,830

9) APPENDICES:

Poster from SfN Society for Neuroscience “Attention-modulated Neural Responses to a Dynamic Visual Selective Attention Task”